IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Samy Ashkar and Jairo Salcedo

Serial No.: 09/981,845 Art Unit: 1647

Filed: October 18, 2001 Examiner: Regina M. Deberry

For: *OSTEOPONTIN-COATED SURFACES AND METHODS OF USE*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBSITUTE APPEAL BRIEF

Sir:

In response to the Notice of Non-Compliant Appeal Brief mailed May 12, 2006, please substitute this Appeal Brief for the one submitted on February 28, 2006. NOTE THAT THIS SUBSTITUTE APPEAL IS NOT IN THE FORMAT THAT IS BELIEVED TO BE CORRECT, BUT WHICH THE EXAMINER HAS REQUIRED. THE TABLE OF CONTENTS HAS BEEN DELETED AND NUMBERING IS NOT AS DESIRED. HOWEVER, IT APPEARS THE EXAMINER WILL NOT ACCEPT THE APPEAL BRIEF EXCEPT IN THIS FORMAT. SINCE THIS HAS ALREADY CAUSED A DELAY OF MONTHS AND INCURRED ADDITIONAL COSTS, IT HAS BEEN SUBMITTED AS THE EXAMINER HAS DEMANDED.

This is an appeal from the final rejection of claims 1-3, 5 and 6 in the Office Action mailed August 8, 2005, in the above-identified patent application. A Notice of Appeal was filed

on November 8, 2005. An Advisory Action was mailed February 15, 2006. **An Appeal brief was filed on August 16, 2004, and a Substitute Appeal Brief on December 2, 2004. The examiner reopened examination on March 17, 2005, in response to the Substitute Appeal Brief. The Commissioner was authorized to charge $165 to Appellant's deposit account in payment of the Appeal Brief filed on August 16, 2004, the fee for filing an Appeal Brief for a small entity. However, the fee for filing an Appeal Brief for a small entity is currently $250.00. The Commissioner was authorized to charge the difference of $85.00, to Deposit Account No. 50-3129, on February 28, 2006.** The Commissioner was also authorized to charge $225.00, the fee for a two month extension of time for a small entity, to Deposit Account No. 50-3129. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Children's Medical Center Corporation in Boston, MA, the assignee of record.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-3, 5 and 6 are pending. Claims 4 and 7-18 have been cancelled. Claims 1-3, 5 and 6 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in an amendment was filed on January 9, 2006, subsequent to the final rejection mailed August 8, 2005. In the advisory action mailed on February 15, 2006, the Examiner indicated that this amendment would be entered. Claim 4 was cancelled in the Amendment filed on June 15, 2005. Claims 7-18 were cancelled in an Amendment filed on November 21, 2003.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 1 defines an active osteopontin peptide fragment comprising an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:15, wherein the peptide binds to at least one integrin receptor on a cell surface selected from the group consisting of αvβ3, αvβ5, 4β1, 2β1, VCAM, ICAM CD44, V3Vx (see at least page 8, lines 7-26 and page 12, lines 4-13).

Dependent claim 2 defines the active peptide fragment of claim 1, wherein the peptide increases cell attachment to a material and increases cell spread (see at least page 8, lines 11-12 and page 53, lines 12-17).

Dependent claim 3 defines the active peptide fragment of claim 1, wherein the peptide binds to at least one integrin receptor on a cell surface selected from the group consisting of VCAM, ICAM CD44, and V3Vx. Dependent claim 5 defines the active peptide fragment of claim 1, wherein the integrin(s) is selected from the group consisting of αvβ3, αv β5, 4β1, and 2β1. Support for claims 3 and 5 can be found at least on page 3, line 27 to page 4, line 14 and page 53, lines 17-21.

Dependent claim 6 defines the active peptide fragment of claim 1, wherein the cell is an osteoprogenitor cell, tumor cell, macrophage, periosteal cell, endothelial cell, epithelial cell, eosinophil, stem cell, limited potential precursor cell, precursor cells committed precursor cell, or differentiated cell (see at least page 8, line 29 to page 9, line 2).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented on appeal is whether claims 1-3, 5 and 6 are enabled under 35 U.S.C. § 112, first paragraph.

(7) ARGUMENTS

(a) The Claimed Invention

Osseointegration is a complex process that involves proliferation, migration, attachment, differentiation, extracellular matrix synthesis, and, finally, mineralization of that matrix. Differentiated cells originate from "primitive" cells called stem cells, which are pluripotent and divide to generate committed precursor cells. After a series of rapid cell divisions, these committed precursor cells develop into differentiated cells, wherein a contribution is made to the surrounding matrix. Driving this process of cellular development is motility and proliferation, which are in turn regulated by increasing or decreasing gradients of, for example, peptides which bind to receptors on the cell surface. The bone trauma generated by implant placement is followed by clot formation, acute inflammation, recruitment and proliferation of stromal cells and their differentiation into osteogenic lineage cells, followed by filling of the defect with bone and, finally, mineralization of the matrix.

Extracellular matrix proteins, especially adhesion molecules, play a role in bone repair and morphogenesis. When cells initially encounter a bio-matrix or extracellular matrix ("ECM"), they will either attach and spread or undergo apoptosis. Adherence to the ECM is a

receptor-mediated process. Cell surface receptors belonging to the integrin superfamily are recognized as critical players in the adhesion to the ECM and are intermediate messengers relaying signals for events such as contact, anchorage, and differentiation. Proteins such as osteopontin or peptides derived from osteopontin, which bind to these receptors, can therefore mediate these cellular processes.

The primary challenge faced in the fabrication of new implants is to increase the rate of osseointegration and the percentage of bone apposition. An enhanced rate of osseointegration and/or augmented percentage of bone apposition around implants increases implant placement indications, and expedites loading time. Recent studies have focused on improving osseointegration of implants by coating the surface with various substances including bone morphological proteins, with varying degrees of success.

The Appellants have isolated active osteopontin peptide fragments that have (1) cell-attachment and (2) cell-spread activity, which, when coated on a material suitable for use as an implant, can increase cell attachment as well as enhance cell spread. The peptides discovered by the Appellants help bring stem cells, precursor cells and differentiated cells into contact with the material. They can also function in bringing tissue remodeling cells such as mesenchymal, macrophages and granulocytes and, in general cells that are involved in osseointegration, into contact with the implant.

(b) Rejection of claims 1-3, 5 and 6 Under 35 U.S.C. § 112, first paragraph, enablement

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the

claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the

breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples. The Supreme Court also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling *In re Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors 'are illustrative, not mandatory. What is relevant depends on the facts.'). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Douglas v. United States* 510 F.2d 364; 184 U.S.P.Q. 613 (Ct. Cl.1975) the Court of Claims noted that a patentee cannot "be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, citing to *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916), wherein the court emphasized that some inventions cannot be practiced without adjustments being made to adapt them to the particular context. In such a situation, a specification is sufficient if it gives adequate guidance to one skilled in the art on how such adjustments are to be made.

Analysis

Claims 1,2, 3, and 5

The issue is not whether one can make and use the claimed peptides; the issue is whether it would require undue experimentation to identify and make peptides having the claimed sequence. This rejection is contrary to the level of skill in the art, which is high, in combination with the information provided in the application as filed.

Claim 1 defines an active osteopontin peptide fragment comprising an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:15, wherein the peptide binds to at least one integrin receptor on a cell surface selected from the group consisting of αvβ3, αvβ5, 4β1, 2β1, VCAM, ICAM CD44, V3Vx.

An active osteopontin peptide refers to an osteopontin fragment that possesses at least one biological activity of naturally occurring osteopontin (see page 11, lines 9-11). The biological activity of osteopontin that the claimed peptides have includes cell attachment and cell spreading activity. Osteopontin performs these biological functions by binding to receptors on the cell surface. It is well known in the art that osteopontin binds to more that one integrin receptor, as is exemplified by Hu, et al, *J. Biol. Chem.* 270(11):26232-38 (1995) (see evidence appendix). The blast 2 sequence comparison (see evidence appendix) shows, for example, that SEQ ID NO 11 and 15 have conserved domains similar to osteopontin. The ability of the peptides recited in claim 1 to bind to ***at least one*** integrin receptor on the cell surface is demonstrated by the ability of anti-integrin antibodies to inhibit cell attachment (for example, SEQ ID NO: 15, (Table 8)). This example clearly demonstrates that the claimed peptides do indeed bind to integrins.

The specific amino acid sequences of the peptides are disclosed at page 8, lines 7-26. The peptides can be made from osteopontin or using recombinant or synthetic techniques. The specification on page 11, lines 9-11 and on page 12, lines 20-31 to page 13, lines 1-5, discloses how osteopontin can be modified to obtain the claimed peptides.

There is no legal requirement that the claimed peptides bind all integrins or all cell types for the peptides to have the specified utility. There is no legal requirement for actual reduction to practice. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.

Since the sequences which are responsible for binding as claimed are described, no undue experimentation would be required. One skilled in the art would simply make peptides including the claimed sequence, and then verify the binding properties using standard, routine techniques as described in the application.

Therefore claim 1, which recites that peptides consisting of SEQ ID Nos. 7-15, bind to at least one intergrin receptor on a cell surface selected from the group of receptors recited in claim 1, claim 3 which recites that the peptide fragments of claim 1 bind to ***at least one*** integrin receptor selected from the integrin receptors listed in claim 3, and claim 5, which recites that the peptide fragments of claim 1 bind to at least on integrin on a cell surface, wherein the integrin is selected from the group consisting of the integrins listed in claim 5, are enabled.

The peptides may be used to increase cell attachment to a biomaterial and to increase cell spreading. The specification on page 13, line 14 to page 14, line 2 describes how to coat the peptides on a material, and the types of materials that may be coated (page 10, lines 16-23 and page 14, lines 22-28). The specification on page 40, lines 4-31, and page 41, lines 1-8, describes

how to measure cell attachment and cell spreading. Example 12 shows that the claimed peptides increase cell attachment and cell spreading. Therefore, it is clear that claim 2, which recites osteopontin peptide fragments which bind to at least one integrin receptor of the surface of a cell and increases attachment to a material and increases cell spreading, is enabled.

Claim 6

Integrins are the principal receptors on animal cells for binding most extracellular matrix proteins, including collagen, fibronectin, and laminin. They are found on the surface of numerous cell types, as demonstrated by textbooks such as *Molecular Biology of the Cell.* IV. Cells in Their Social Context. 19. Cell Junctions, Cell Adhesion, and the Extracellular Matrix, Garland Publishing (1994)). As is exemplified in Hu, et al, *J. Biol. Chem.* 270(11):26232-38 (1995) and Tuck, et al, J. Cell. Biochem., 78:465-75 (2000) (see evidence appendix), osteopontin will bind to different cell types that express its receptors. The cells employed by Hu, et al. are carcinoma cells, whereas Tuck, et al. employs epithelial cells. These references demonstrate that osteopontin will bind to at least one of its receptors on a cell expressing the receptor.

Since the claimed active osteopontin peptide fragments bind integrins, and since integrins are expressed on diverse cell types, the claimed peptides should bind diverse cell types expressing integrins. The specification describes a number of cell types that may be regulated using the active osteopontin peptides fragments (page 8, line 29 to page 9, line 2). Example 12 and Table 8 on pages 53-55, demonstrate that plates coated with each of, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14 or SEQ ID NO:15, bind to osteoprogenitor cells and have significantly increased cellular attachment and spread as compared to control (uncoated plates). This is shown in Table 8 with SEQ ID NO: 15, to be due to binding to the $\alpha v\beta 3$ receptor.

As emphasized by the examiner, osteoprogenitor cells are able to spread in the presence of antibodies to CD44 and β1, showing that SEQ ID NO: 15 does not bind to these receptors in a manner that is supportive of osteoblast function. However, the only conclusion that can be drawn from table 8 is that cell attachment and spread are not predominantly controlled by CD44 and β1. The study by Tuck et al., clearly supports this reasoning. Anti αvβ5 and β1 antibodies completely blocked migration of 21PT and 21NT cells but had no effect on migration of MDA-MB-435 cells (all mammary epithelial cells). Osteopontin-induced migration of MB-435 cells was completely blocked by anti- αvβ3 antibodies. This is not because osteopontin does not bind to these integrins (Hu, et al., states that it does), but because migration in these cell lines is dependent on different integrins. Furthermore, more malignant MDA-MB-435 cells express αvβ3 integrins, while less malignant cells do not (see Hu, et al. page 471). Similar to this reasoning, Noonan, et al, J. Orthop. Res., 14(4):573-81 (1996) (abstract; see evidence appendix), states that osteoprogenitor cells express low levels of CD44. These references in combination demonstrate that osteopontin or any peptide capable of binding to osteopontin receptors can perform the same biological function in different cell types depending on the receptor predominantly expressed by that cell.

The claims are drawn to peptides that bind to at least one integrin receptor to increase cell binding and spread. Table 8 demonstrated an 87% and 89% spread of osteoprogenitor cells in the presence of anti-CD 44 and anti-β1 antibodies, not a 100% spread. The fact that a peptide binds to at least one integrin receptor, and improves cell attachment and spread, does not exclude that fact that it could bind more than one integrin receptor, or that the effect could be concentration dependent, so that the amount of cell spread induced by a particular receptor is commensurate to the level of expression of that receptor. This is shown on table 8 and supported

by Noonan, et al. A conclusion cannot be drawn that the peptides do not bind to CD-44 and β1 considering the fact that osteoprogenitor cells express different integrin receptors at different levels. It would be expected by one skilled in the art that the amount of cell spreading in response to binding to a particular integrin receptor would be proportional to the level of expression of that receptor, if more that one type of receptor is expressed that can bind to the same peptide.

Horton, *Int. J. Biochem. Cell. Biol.* 29(5):721-25 (1997), states that αvβ3 expression has been shown in numerous cell types (see section entitled "Biosynthesis and Tissue Distribution" on page 722). Even though Horton does specifically teach the presence of αvβ3 on stem cells, there are art recognized techniques for determining the integrin expression profile of a cell, and the integrins expressed by the cells recited in claim 6, such as αvβ3, are known in the art. A patent need not teach, and preferably omits, what is well known in the art.

Osseointegration is a complex process and involves wound healing and osteogenesis. The cells involved in theses processes, such as those listed claim 6, are known in the art, and are defined in the specification (see age 2, line 29 to page 4, line 14, page15, lines 10-20 and page 29, lines 3-13,). Because of the ubiquitous expression of integrins on cells, and the fact that the specification clearly demonstrates the ability of the peptides to bind to ***at least one*** integrin on a cell surface, claim 6, reciting that the claimed peptides bind to at least one integrin receptor on a cell, wherein the cell is selected from the cells listed claim 6, is enabled.

(c) Summary and Conclusion

The examiner has provided only speculation and unsupported arguments for why the specification is not enabling. It is well established that a specification is presumed to be enabling. A *prima facie* case of non-enablement can only be made upon a showing of evidence,

not argument, of why one skilled in the art would not be able to make and use the claimed subject matter. Even assuming *arguendo* that the examiner has done so, appellants have rebutted this with reference to both the specification and the literature. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988). It is clear from the direction and guidance given by the specification, the presence of working examples, the state of the prior art and the relative skill of those in the art, that one of ordinary skill in the art could make the claimed peptides which bind to at least one integrin receptor a cell surface, and use the peptides to increase the cell attachment to a biomaterial and cell spread.

For the foregoing reasons, Appellants submit that claims 1-3, 5 and 6 are enabled.

Respectfully submitted,

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(8) Claims Appendix: Claims On Appeal

1. An active osteopontin peptide fragment comprising an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:15, wherein the peptide binds to at least one integrin receptor on a cell surface selected from the group consisting of $\alpha v\beta 3$, $\alpha v\beta 5$, $4\beta 1$, $2\beta 1$, VCAM, ICAM CD44, V3Vx.

2. The peptide fragment of claim 1, wherein the peptide increases cell attachment to a biomaterial and increases cell spread.

3. The peptide fragment of claim 1, wherein the peptide binds to at least one integrin receptor on a cell surface selected from the group consisting of VCAM, ICAM CD44, and V3Vx.

5. The peptide fragment of claim 1 wherein the integrin(s) is selected from the group consisting of $\alpha v\beta 3$, $\alpha v\ \beta 5$, $4\beta 1$, and $2\beta 1$.

6. The peptide fragment of claim 1 wherein the cell is selected from the group consisting of osteoprogenitor cells, tumor cells, macrophages, periosteal cells, endothelial cells, epithelial cells, eosinophils, stem cells, limited potential precursor cells, precursor cells, committed precursor cells, and differentiated cells.

(9) Evidence Appendix

I. Evidence submitted with Amendment May 11, 2004

Hu, et al., J. Biol. Chem. 270(44):26232-26238 (1995)

Tuck, et al., J. Cell. Biochem. 78:465-475 (2000)

II. Evidence submitted with Substitute Appeal Brief December 2, 2004

Noonan, et al., J. Orthop. Res. 14(4):573-581 (1996) (Abstract)

III. Evidence submitted with Amendment June 15, 2005

Webster's Third New International Dictionary definition of "fragment"

Horton, Intl. J. Biochem. 29(5):721-725 (1997)

Blast 2 sequences comparing SEQ ID No: 11 and SEQ ID NO:15

NCBI Conserved Domain Search SEQ ID NO:11, SEQ ID NO:15

(10) Related Proceedings Appendix

None